REMARKS

Claims 1-40 are pending in the instant application. Claims 1-40 have been rejected.

Rejection of Claims 1-9 and 22-34 under 35 USC §103(a)

The Examiner has rejected Claims 1-9 and 22-34 under 35 USC §103(a), as being unpatentable over Cragoe Jr. *et al.*, U.S. 4,731,471 and/or Conn *et al.*, U.S. 4,704,472. Specifically, the Examiner stated that:

> It is noted that while the cited prior art may not teach R3 and R10 groups that are heterocyclic, the references do however teach a number of other substituent combinations, including no substitution at the 4 position, that do fall within the scope of the claimed invention.

Applicants respectfully traverse this rejection. To establish a *prima facie* case of obviousness, three basic criteria must be met: a suggestion or motivation to modify the reference or to combine reference teachings; there must a reasonable expectation of success; and the references must teach or suggest all claim limitations. *See*, MPEP 2143. Applicants assert that none of these three criteria are met by the Cragoe and Conn references.

The Cragoe and Conn art must be considered *in its entirety*, i.e. as a whole, including portions that would lead away from the claimed invention, see MPEP 2141.02 (emphasis added). The Cragoe and Conn references require specific substitution for anti-edemic activity that is not disclosed in Applicants' claims. For example, Applicants claim compounds that must be substituted at R^3 (position 4 on the tetrahydrofluorenone ring system), while Cragoe and Conn do not teach any substitution at position 4 on the tetrahydrofluorenone ring system. Likewise, Applicants teach substitution at R^{10} (position 9a on the tetrahydrofluorenone ring system), while Cragoe teaches C_{1-6} hydroxyalkyl, C_{1-6} haloalkyl, C_{1-6} acyloxyalkyl or C_{1-6} alkoxyalkyl at position 9a. Cragoe further teaches at column 3, lines 24-35, that:

> The compounds of this invention are of particular value since the *novel functional 9a-substituent is designed to import highly desirable*

> *properties*. The unique character of these substituents is intended to impart increased capability to cross the blood-brain barrier while retaining *potent intrinsic anti-edemic activity*. The 9a-substituents were selected for their known ability to affect lipophilicity, protein binding, etc. which are known to influence the tendency of drugs to cross the blood-brain barrier. (emphasis added)

Thus, Cragoe teaches that these derivatives are useful in the treatment of brain edema, and explains that the desired anti-edemic activity is achieved due to the *novel functional 9a-substituents* disclosed. Clearly, a medicinal chemist skilled in the art would not look to Cragoe for instruction in modifying or making selective estrogen receptor modulators.

Applicants insist that there is no suggestion or motivation to modify the references. "There are three possible sources for a motivation to combine references: the nature of the problem to be solved, the teachings of the prior art and the knowledge of persons of ordinary skill in the art." *In re Rouffet,* 149 F.3d 1350, 1357, 47 USPQ2d 1453, 1457-58 (Fed Cir 1998). In the present invention, the problem to be solved involves estrogen receptor modulation, and the teachings of the analogous prior art would include utilization of estrogen and other SERMs, such as tamoxifen. If faced with such a problem, one of ordinary skill in the art would look to references involving estrogen receptor modulation and teachings disclosed therein.

The Cragoe and Conn references are nonanalgous art. "In order to rely on a reference as a basis for rejection of an application's invention, the reference must either be in the field of the applicant's endeavor or, if not, then be reasonably pertinent to the particular problem with which the inventor was concerned." See MPEP 21412.01(a). The problem to be solved in the Cragoe and Conn references is the the treatment of brain edema. The teachings contained therein relate to compounds and synthetic methodologies for the treatment and prevention of injury to the brain and edema due to trauma. The compounds disclosed therein reduce brain edema via an anion transport inhibition mechanism. Those compounds are able to regulate the chloride channels in astrocyte cells because of their specific substitution patterns (e.g., substitution at position 9a). The disclosure does not discuss, teach nor suggest the use of the compounds and

methodologies disclosed therein for any other uses, including estrogen receptor modulation. An endocrinologist or medicinal chemist researching in the nuclear receptor field would not look to the Cragoe and Conn references for guidance. Furthermore, they would not be motivated to synthesize the compounds disclosed therein in their research efforts.

Likewise, there is no reasonable expectation of success that the compounds disclosed in Cragoe and Conn could be modified to become useful as estrogen receptor modulators. An endocrinologist or medicinal chemist would not believe that compounds disclosed as having utility for the treatment of brain injury could be modified to become useful in the treatment of disorders related to estrogen functioning. Furthermore, one skilled in the art would not believe that compounds taught as chloride transport blockers in the astroglia would have utility in modulating estrogen receptors.

Applicants would also like to highlight the fact that the Cragoe and Conn references do not teach nor suggest all of the claim limitations disclosed herein. The genus of compounds disclosed in the Cragoe and Conn references do not overlap with the genus claimed in the present invention, nor teach each limitation suggested in the claims describing the compounds themselves. Furthermore, the cited references do not describe the methods of treatment disclosed in the instant specification. Thus, Cragoe and Conn do not meet the criteria set out in MPEP 2143.

Since the three basic criteria necessary for establishing a *prima facie* case of obviousness have not been met, Applicants respectfully request that the rejection of Claims 1-9 and 22-34 under §103 be withdrawn.

Rejection of Claims 10-21 and 36-40 under 35 USC §112, first paragraph

The Examiner has rejected Claims 1-9 and 22-31 under 35 USC §112, first paragraph, for allegedly failing to comply with the written description requirement. Specifically, the Examiner stated that:

> The instant specification does not adequately describe the nexus between the modulation of the estrogen receptor and a useful treatment of a disease/condition. Modification of a receptor involves antagonism, inhibition, agonism and others. These modulators are

sometimes opposite reactions to the same receptor. It is not seen where the instant specification adequately describes the nexus between the modulation of the estrogen receptor and a useful treatment of a single disease or condition.

Applicants respectfully traverse this rejection. Estrogen receptors are found throughout the body in many tissues. Estrogen plays a role in a variety of bodily functions, including maintenance of bone mass and sustenance of estrogen-dependent cancers. Naturally occurring and synthetic estrogens have broad therapeutic utility, including relief of post-menopausal symptoms and treatment of osteoporosis. What is desired in the art are therapies that can produce the same positive responses as estrogen replacement therapy without the negative side effects. The present invention claims such therapeutics.

The Examiner notes that "modification of a receptor involves antagonism, inhibition, agonism and others." Agonism of the estrogen receptor can lead to a desired result in certain tissues (i.e. increase in bone mass) while antagonism is the preferred functionality in others (i.e. non-proliferation of tissue in the breast or uterus). Accordingly, selective estrogen receptor modulators ("SERMs") that can selectively agonize in specific tissues and antagonize in other tissues are highly desired in the art. Examples of SERMs currently marketed include: tamoxifen, which is an ER antagonist in breast tissue but an ER agonist is bone and uterine tissue; and raloxifene, which is an ER antagonist in breast tissue, and an ER agonist in bone but not uterine tissue.

The nexus between estrogen receptor modulation and the useful treatment of particular diseases and conditions is known in the art. There are many references known and understood by those skilled in the art that support the utility of SERMs in the treatment of the claimed disorders. Some are included for your review.

For example, the utility of SERMs for the treatment of breast, uterine or prostate cancer is known in the literature, see T.J. Powles, "Breast cancer prevention," Oncologist 2002; 7(1):60-4; Park, W.C. and Jordan, V.C., "Selective estrogen receptor modulators (SERMS) and their roles in breast cancer prevention." Trends Mol Med. 2002 Feb;8(2):82-8; Wolff, A.C. *et al.*, "Use of SERMs for the adjuvant therapy of early-stage breast cancer," Ann N Y Acad Sci.

2001 Dec;949:80-8; Steiner, M.S. *et al.*, "Selective estrogen receptor modulators for the chemoprevention of prostate cancer," Urology 2001 Apr; 57(4 Suppl 1):68-72.

The utility of SERMS in the treatment of metastatic bone disease is known in the literature, see, Campisi, C. *et al.*, "Complete resoultion of breast cancer bone metastasis through the use of beta-interferon and tamoxifen," Eur J Gynaecol Oncol 1993;14(6):479-83.

The utility of SERMS in the treatment of gynecomastia is known in the literature, see, Ribeiro, G. and Swindell R., "Adjuvant tamoxifen for male breast cancer." Br J Cancer 1992;65:252-254; Donegan, W., "Cancer of the Male Breast," JGSM Vol. 3, Issue 4, 2000.

The utility of SERMs to treat or prevent osteoporosis, hypercalcemia of malignancy, bone loss or bone fractures is known in the literature, see Jordan, V.C. *et al.*, "Selective estrogen receptor modulation and reduction in risk of breast cancer, osteoporosis and coronary heart disease," Natl Cancer Inst 2001 Oct; 93(19):1449-57; Bjarnason, NH *et al.*, "Six and twelve month changes in bone turnover are realted to reduction in vertebral fracture risk during 3 years of raloxifene treatment in postemenopausal osteoporosis," Osteoporosis Int 2001; 12(11):922-3; Fentiman I.S., "Tamoxifen protects against steroid-induced bone loss," Eur J Cancer 28:684–685 (1992); Rodan, G.A. *et al.*, "Therapeutic Approaches to Bone Diseases," Science Vol 289, 1 Sept. 2000.

The use of SERMs to treat periodontal disease or tooth loss in a mammal is known in the literature, see Rodan, G.A. *et al.*, "Therapeutic Approaches to Bone Diseases," Science Vol 289, 1 Sept. 2000 pp. 1508-14.
The use of SERMs to treat Paget's disease in a mammal is known in the literature, see Rodan, G.A. *et al.*, "Therapeutic Approaches to Bone Diseases," Science Vol 289, 1 Sept. 2000 pp. 1508-14.

The use of SERMS to treat uterine fibroids, or uterine leiomyomas, is known in the literature, see Palomba, S., et al, "Effects of raloxifene treatment on uterine leiomyomas in postmenopausal women,"
Fertil Steril. 2001 Jul;76(1):38-43.

The use of SERMs to treat obesity is known in the literature, see Picard, F. *et al.*, "Effects of the estrogen antagonist EM-652.HCl on energy

balance and lipid metabolism in ovariectomized rats," Int J Obes Relat Metab Disord. 2000 Jul;24(7):830-40.

The use of SERMs to treat cartilage degeneration, rheumatoid arthritis or osteoarthritis is known in the literature, see Badger, A.M. *et al.*, "Idoxifene, a novel selective estrogen receptor modulator, is effective in a rat model of adjuvant-induced arthritis." J Pharmacol Exp Ther. 1999 Dec;291(3):1380-6.

The use of SERMs to treat endometriosis is known in the art, see Steven R. Goldstein, "The Effect of SERMs on the Endometrium," Annals of the New York Academy of Sciences 949:237-242 (2001).

The use of SERMs to treat urinary incontinence is known in the art, see, Goldstein, S.R., "Raloxifene effect on frequency of surgery for pelvic floor relaxation," Obstet Gynecol. 2001 Jul;98(1):91-6.

The utility of SERMs in treating or preventing cardiovascular disease, restenosis, lowering levels of LDL cholesterol and inhibiting vascular smooth muscle cell proliferation is known in the art, see Nuttall, ME *et al.*, "Idoxifene: a novel selective estrogen receptor modulator prevents bone loss and lowers cholesterol levels in ovariectomized rats and decreases uterine weight in intact rats," Endocrinology 1998 Dec; 139(12):5224-34; Jordan, V.C. *et al.*, "Selective estrogen receptor modulation and reduction in risk of breast cancer, osteoporosis and coronary heart disease," Natl Cancer Inst 2001 Oct; 93(19):1449-57; Guzzo JA., "Selective estrogen receptor modulators--a new age of estrogens in cardiovascular disease?," Clin Cardiol 2000 Jan;23(1):15-7; Simoncini T, Genazzani AR., "Direct vascular effects of estrogens and selective estrogen receptor modulators," Curr Opin Obstet Gynecol 2000 Jun;12(3):181-7.

The utility of SERMs to prevent the impairment of cognitive functioning is known in the art, see Yaffe, K., K. Krueger, S. Sarkar, *et al.* 2001. Cognitive function in postmenopausal women treated with raloxifene. N. Eng. J. Med. **344:** 1207-1213.

Thus, Applicants assert that an endocrinologist understands the nexus between estrogen receptor modulation and the treatment of disorders claimed herein and knows when to proscribe a SERM. The disclosures in the instant application and in the known literature provide ample teaching of disorders treatable with SERMs.

Accordingly, Applicants respectfully request the rejection of claims 10-21 and 36-40 under 35 USC §112, first paragraph, be withdrawn.

Rejection of Claims 10-21 and 36-40 under 35 USC §112, first paragraph

The Examiner has rejected Claims 1-9 and 22-31 under 35 USC §112, first paragraph, for allegedly failing to comply with the enablement requirement. Specifically, the Examiner stated that:

> Thus, the specification fails to provide sufficient support of the broad use of the compounds of claim 1 for the treatment of any disease or condition in any mammal. As a result necessitating one of ordinary skill to perform an exhaustive search for which diseases can be treated by which compound of claim 1 in order to practice the claimed invention.
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> ...
>
> Therefore in view of the Wands factors and In re Fisher (CCPA 1970) discussed above, to practice the claimed invention herein, one of ordinary skill in the art would have to engage in undue experimentation to test which diseases can be treated by the compounds of the instant claims with no assurance of success.

Applicants respectfully traverse this rejection. In order to make a rejection based upon lack of enablement, *the Examiner has the initial burden* to establish a reasonable basis to question the enablement provided for the claimed invention (MPEP §2164.04). "A specification disclosure which contains a teaching...must be taken as being in compliance with the enablement requirement of 35 U.S.C. 112, first parpagraph, *unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support*" (MPEP 2164.04, emphasis added). The Examiner has not met the initial burden of establishing a reasonable basis to question the enablement provided in the specification.

Assuming arguendo that the Examiner had met the initial burden of proof, Applicants have provided ample guidance how to make and use the claimed invention. The specification contains general schemes on pages 22-36 to make the

claimed compounds that would allow the skilled artisan access to any of the claimed compounds by simple permutations known in the art. In addition, there are over 100 pages of specific examples (pages 37-138) taught in the specification, and an assay for determining estrogen receptor binding. Additionally, typical formulations and dosing ranges to administer the compounds to patients in need of such treatment are provided.

MPEP 2164.01(c) recites "if a statement of utility in the specification contains within it *a connotation of how to use* and/or the art recognizes that standard modes of administration are known and contemplated, 35 USC 112 is satisfied" (emphasis added). Based upon the information provided in the specification, Applicants have satisfied the condition by explaining how to use the compounds of the instant invention; namely that they modulate estrogen receptors. As is stated in the specification and described in the literature, estrogen receptor modulators play a role in many important physiological functions, such as bone resorption, regulation of lipid levels, and playing a role in estrogen dependent cancers. Evidence that the claimed compounds have the asserted utility can be found in the myriad of papers described in the previous section and enclosed herewith.

The Examiner further alleges that one skilled in the art would have to "engage in undue experimentation to test which diseases can be treated by the compounds of the instant claims with no assurance of success." MPEP 2164.01(c) states that "if one skilled in the art, based on knowledge of compounds having *similar physiological or biological activity*, would be able to discern an appropriate dosage or *method of use* without undue experimentation, this would be sufficient to satisfy 35 USC 112" (emphasis added). Compounds having similar physiological or biological activity to those claimed in the instant invention would be currently marketed SERMs. Those skilled in the art readily recognize how to use and prescribe SERMs. For example, raloxifene, marketed as EVISTA®, is a SERM and is prescribed to patients to build bone, without negatively affecting breast or uterine tissue. Raloxifene is also reported to lower total cholesterol by 7% and LDL by 11%. Tamoxifen, another SERM, is also currently marketed for the treatment of breast cancer.

The amount of experimentation needed to use the disclosed compounds as estrogen receptor modulators to treat disorders associated with

estrogen receptor functioning is not undue experimentation. Routine screening ***is not*** equivalent to undue experimentation. "Enablement is not precluded by the necessity for some experimentation such as routine screening." *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). In the instant case, Applicants have described representative disorders that are treatable with compounds of the instant invention (for example, page 3 lines 27-35) and generally described how to administer the compounds of the instant invention (for example, page 20, line 17 – page 22, line 16). Clearly one skilled in the art would not require undue experimentation as alleged by the examiner.

The examiner has the difficult burden of showing conclusively that the application is not enabled. Applicants submit that this burden has not been met. Nevertheless, one skilled in the art, utilizing current knowledge and the disclosures in the instant specification, would be able to use and make the claimed invention without undue experimentation. Accordingly, Applicants respectfully request the rejection of claims 10-21 and 36-40 under 35 USC §112, first paragraph, be withdrawn.

If a telephonic communication with the Applicants' representative will advance the prosecution of the instant application, please telephone the representative indicated below. Applicants believe no additional fees are due but the Commissioner is authorized to charge any fees required in connection with this response to Merck Deposit Account No. 13-2755.

Respectfully submitted,

By Nicole M Beeler

Nicole M. Beeler
Reg. No. 45,194
Attorney for Applicants
MERCK & CO., INC.
P.O. Box 2000
Rahway, New Jersey 07065-0907
(732) 594-1077

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